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MAIL STOP - PCT  
Docket No. 27707U

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Inventor: KOBAYASHI, et al.                      Art Unit:        XXXX  
Appl. No.:        10/594,544                      Examiner:        XXXX  
Filing Date:     September 28, 2006              Conf. No.:       1924  
Intl. Appl. No.:        PCT/JP2004/004699  
Intl. Filing Date:    March 31, 2004  
Title:        **REVERSIBLY IMMORTALIZED MAMMALIAN LIVER CELLS AND USE  
              THEREOF**

**TRANSMITTAL LETTER**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Sir:

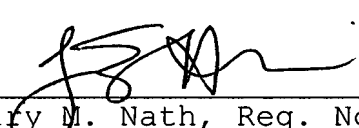
Submitted herewith for filing in the U.S. Patent and Trademark Office is the following:

1. Submission of Documents to Supplement Filing Documents under 35 USC 371;
2. PCT/IB/338 (Notification of Transmittal of Copies of Translation of the International Preliminary Report on Patentability);
3. PCT/IB/373 (International Preliminary Report on Patentability); and
4. PCT/ISA/237 (Written Opinion of the International Searching Authority).

The Commissioner is hereby authorized to charge any deficiency or credit any excess to Deposit Account Number 14-0112.

Respectfully submitted,  
**THE NATH LAW GROUP**

May 14, 2007  
**THE NATH LAW GROUP**  
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From the INTERNATIONAL BUREAU

**PCT**

NOTIFICATION OF TRANSMITTAL  
OF COPIES OF TRANSLATION  
OF THE INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY  
(CHAPTER I OR CHAPTER II  
OF THE PATENT COOPERATION TREATY)  
(PCT Rules 44bis.3(c) and 72.2)

To:

ASAHINA, Sohta  
NS Building  
2-22, Tanimachi 2-chome  
Chuo-ku, Osaka-shi  
Osaka 5400012  
JAPON

Date of mailing ( <i>day/month/year</i> ) 07 December 2006 (07.12.2006)	
Applicant's or agent's file reference FP-8667PCT	<b>IMPORTANT NOTIFICATION</b>
International application No. PCT/JP2004/004699	International filing date ( <i>day/month/year</i> ) 31 March 2004 (31.03.2004)
Applicant KOBAYASHI, Naoya et al	

**1. Transmittal of the translation to the applicant.**

The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).



The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

**2. Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

None

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

**3. Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. +41 22 338 82 70	Authorized officer  Masashi Honda  Facsimile No. +41 22 338 82 70
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference FP-8667PCT	<b>FOR FURTHER ACTION</b>	See item 4 below
International application No. PCT/JP2004/004699	International filing date ( <i>day/month/year</i> ) 31 March 2004 (31.03.2004)	Priority date ( <i>day/month/year</i> )
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant KOBAYASHI, Naoya		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).
2. This REPORT consists of a total of 4 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- |                                     |              |   |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report   |
| <input type="checkbox"/>            | Box No. II   | Priority  |
| <input type="checkbox"/>            | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/>            | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application  |
| <input type="checkbox"/>            | Box No. VIII | Certain observations on the international application   |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. +41 22 338 82 70	Date of issuance of this report 29 November 2006 (29.11.2006)  Authorized officer  <div style="text-align: center; font-weight: bold; font-size: 1.2em;">Masashi Honda</div>  e-mail: pt08@wipo.int
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# PATENT COOPERATION TREATY

TRANSLATION

From the  
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

Date of mailing  
(day/month/year)

Applicant's or agent's file reference

**FP-8667PCT**

**FOR FURTHER ACTION**

See paragraph 2 below

International application No.

**PCT/JP2004/004699**

International filing date (day/month/year)

**31.03.2004**

Priority date (day/month/year)

International Patent Classification (IPC) or both national classification and IPC

Applicant

**KOBAYASHI, Naoya**

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP

Authorized officer

Facsimile No.

Telephone No.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/JP2004/004699

Box No. I      Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language  
\_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material  
☒ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material  
☐ in written format  
☒ in computer readable form
  - c. time of filing/furnishing  
☐ contained in the international application as filed.  
☒ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/JP2004/004699

**Box No. V** Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

**1. Statement**

Novelty (N)	Claims	<u>1-8</u>	YES
	Claims	_____	NO
Inventive step (IS)	Claims	_____	YES
	Claims	<u>1-8</u>	NO
Industrial applicability (IA)	Claims	<u>1-8</u>	YES
	Claims	_____	NO

**2. Citations and explanations:**

Document 1: KOBAYASHI, N. et al., Prevention of acute liver failure in rats with reversibly immortalized human hepatocytes. Science. 18 February, 2000, Vol. 287, pages 1258-1262

Document 2: KOBAYASHI, N. et al., Establishment of a tightly regulated human cell line for the development of hepatocyte transplantation. Hum Cell. 2000 March, Vol. 13 (1), pages 7-13

Document 3: Naoya KOBAYASHI et al., "Kanzo to Saisei Iryo", Saisei Iryo, 2002 November, Vol. 1 (2), pages 23-28

Document 4: Naoya KOBAYASHI et al., "Kansaibo Ishoku ni Muketa Fushika Hito Kansaibokabu no Juritsu", Cell Technology, 2000 June, Vol. 19 (6), pages 864-868

**Concerning claims 1-8:**

The subject matters of claim 1-8 do not appear to involve an inventive step in view of documents 1-4.

Documents 1-4 disclose reversibly immortalized mammalian hepatocytes containing an immortalizing gene and a suicide gene sandwiched between a pair of site-specific recombination sequences.

The difference between the invention described in claims 1-8 and the invention disclosed in documents 1-4 is whether the suicide gene is located between the site-specific recombination sequences or not; however, both inventions are common to each other in that they have a dual safety mechanism whereby the immortalizing gene can be removed by a recombination reaction and there exists the suicide gene. Whether to make the suicide gene removable or not is merely a matter that a person skilled in the art could easily decide in consideration of the safety of the cell.